Exhibit 1

Exhibit 1

Los Angeles Times VIEW Friday, December 5, 1986/Pa

Vest Coast's st Pancreas Transplant

By SUE HORTON

It certainly wasn't a gourmet ast, but to Clara Clements it emed like one. There was soup d chicken, rice and bread, nd. Clements recounted with light. "There was coffee cake, ad a piece of cake."

For 20 years since coming wn with diabetes, Clements, a -year-old Glendale resident, d been on a restricted diet in ich sugars and starchy foods re taboo.

Then last month, she had a ncreas transplant at UCLA edical Center, the first such eration performed on the est Coast. On Thursday, ements was well enough to ave the hospital after a 3½- ek stay.

First Unrestricted Dinner

After the operation, Clements d something most diabetics n't even dare hope for—a ealthy pancreas capable of oducing sufficient insulin to ntrol her blood-sugar levels. veral days after the operation e ate her first unrestricted nner.

"When she saw that first eal, her eyes gleamed," said . Patrick Soon-Shiong, the CLA surgeon who performed ements' transplant. "She told e she had been waiting for that y for 20 years. That is what is operation is all about—im- oving the quality of life for tients with severe diabetes."

Pancreas transplant surgery still in its infancy. To date, ly about 900 pancreas trans- ants have been performed rldwide. Currently, four pan-

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TRANSPLANT: New Hope

Continued from Page 1

creas transplant centers are operating in the United States, and UCLA is the only center on the West Coast performing the procedure.

The pancreas, a six-inch-long organ located behind the stomach, regulates the body's conversion of sugars and carbohydrates to energy by secreting the enzyme insulin to adjust the level of sugar in the blood.

In diabetics, the pancreas either does not manufacture sufficient quantities of insulin or the insulin it manufactures does not do an adequate job of metabolizing sugars and carbohydrates. Patients like Clements, with severe cases of diabetes, must therefore inject themselves regularly with insulin.

Serious Complications

But daily insulin injections cannot mimic the way a normal pancreas secretes the appropriate amount of insulin during the day in response to rising and falling blood-sugar levels. Because injections are less effective, diabetics can develop serious complications such as heart disease, blindness, stroke, kidney failure and severe circulatory problems which can lead to limb amputation.

Soon-Shiong said that pancreas transplants are the most difficult type of organ transplant. "The pancreas is an extremely delicate organ," he said. "To harvest the organ from the donor requires a four- to five-hour operation." If the pancreas is damaged during the operation, it can secrete the digestive juices which, in effect, cause the pancreas to destroy itself."

Implanting the pancreas in the patient requires another four- to five-hour operation, during which numerous small blood vessels must be connected. The patient's old pancreas is left in place, and the new pancreas is placed lower in the abdomen near the groin area.

Performing the transplant on Clements was difficult but very exciting, Soon-Shiong said. "After we [connected blood vessels to] the organ, we saw it literally come to life and pulsate on the operating table," he said.

A successful connection of the organ is not the only obstacle with pancreas transplants. After surgery, the patient must be carefully monitored, because, as with other types of organ transplants, there is

Los Angeles Tim

a chance the new organ will be rejected.

Indeed, two weeks after receiving her new organ, Clements showed signs of rejecting it. "We caught it early, and were able to treat the rejection episode [with drugs] in the hospital," Soon-Shiong said. Until her new organ recovers fully, Clements is taking some insulin again, but Soon-Shiong estimates that within several weeks her pancreas will again be fully functional.

"She is progressing very rapi ly," he said. "I estimated that aft one week I could halve the dose insulin she required after the reje tion episode. Instead, I was able halve it after two days."

The one-year patient survi rate after a pancreatic transplant about 95%, a UCLA spokesma said. After two years, between 65 and 70% of transplant patien

Please see PANCREAS, Page

S ANGELES
Herald Examiner

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Double transplant renews hope

Diabetic who thought he'd die young is busy planning his future

By Betsy Bates
Herald Examiner medical writer

The day Robert Katzman's beeper went off in a Thrifty Drug Store, someone was chitchatting on the only pay phone outside.

The yakker didn't know Katzman's call was, for him, a matter of life and death. Word had finally come of a donor.

Fifteen hours later, the 33-year-old diabetic would be lying in the intensive care unit at UCLA Medical Center, the West's first pancreas-kidney transplant patient to receive both organs in a single surgery.

Dependent on insulin injections for 19 years, Katzman was typical of about 1 million juvenile-onset diabetics in the U.S. whose pancreases are unable to manufacture insulin. The hormonal repercussions of the disease, including non-insulin dependent diabetes that afflicts 10 million people, take a heavy toll: 300,000 die each year and 5,000 go blind. Diabetics constitute 25 percent of kidney dialysis patients, 45 percent of all non-traumatic amputees and more than twice as many victims of heart disease and strokes than the average population.

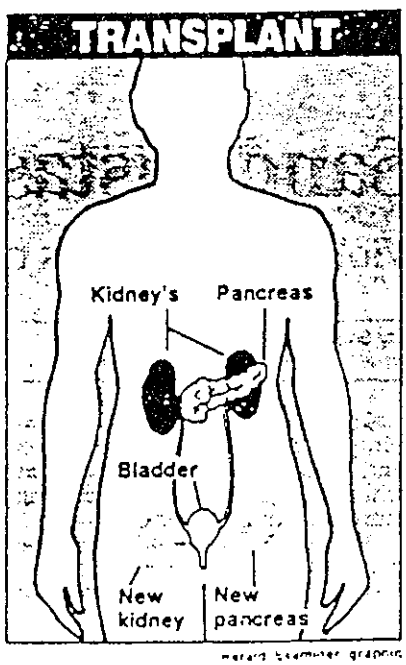
Costing $14 billion annually, diabetes is a high priority disease since its victims suffer health problems virtually throughout their lives.

Pancreas transplants, combined with kidney transplants when those organs have also failed, are seen by many as a way to end the cycle of insulin and dialysis treatments, stopgap measures that inevitably can't do the job that the organs themselves were meant to do.

Roughly 300 of the combined transplants have been done worldwide, but Katzman's was the first attempted here. Two additional patients are awaiting donors now.

Chris Gulker-Herald Examiner

UCLA's Eileen DeMayo takes Robert Katzman's blood pressure



Herald Examiner graphics

"I was sinking pretty fast," recalled Katzman. "If I had done this, I probably wouldn have survived this year."

Diagnosed with diabetes at after he lost 50 pounds in a mont and found himself perpetuall thirsty, Katzman combatted h disease with daily insulin injec tions despite a fear of needles Adolescence was a trial, as h tried to fit in as the sickly kid wh couldn't take gym.

"I didn't understand my di betes completely, and sometime I'd deny it. We'd go to Bob (restaurant) and I ate the frenc fries and drank the shakes lik everyone else, not knowing ho much damage I was doing," h said.

After graduating from Missio College, Katzman became a nutri tion counselor and came to grip with the limits his condition would place on his life. He ar into management for Nutri-Sy tem Weight Loss Centers an toyed with the idea of going t law school.

By April of last year, the plans seemed like pipe dr-ams

Transplant, A-9 ▶

Exhibit 2

Exhibit 2

Los Angeles Times

CIRCULATION: 1,138,353 DAILY / 1,521,197 SUNDAY

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DAILY 35¢
DESIGNATED AREAS HIGHER

Artificial Pancreas Is Implanted in Diabetic

■ Medicine: Experiment is first in U.S. If successful, procedure may eliminate the need for insulin shots.

By THOMAS H. MAUGH II
TIMES SCIENCE WRITER

Physicians at St. Vincent Medical Center announced Thursday that they have begun the first U.S. human trials of an artificial pancreas that they hope will someday free diabetics from the need for insulin injections.

The artificial pancreas was implanted last week in the abdomen of 38-year-old Steven Craig of Lake Isabella, who has been diabetic for more than 30 years and has been unable to work for seven years because of complications of the disease. It is the first of 20 such implants the hospital is planning during the next two years.

Dr. Patrick Soon-Shiong of St. Vincent and USC implanted insulin-secreting islet cells from cadavers. The cells were encapsulated in a porous membrane that keeps them safe from attack by Craig's immune system.

Soon-Shiong hopes that the implanted cells will permit Craig to forgo his daily insulin shots and prevent progression of his symptoms but noted that it will be months before doctors can assess the implant's value. "This is the very first step on a long, exciting but unexplored road," he said.

If the device is shown to be safe and effective, the researchers hope to use pigs as islet donors, which would theoretically provide enough cells to treat all 1.4 million insulin-dependent diabetics in the United States.

"This is really exciting," said biochemist Joan Harmon of the National Institute of Diabetes and Digestive Disease. "We've been waiting for this for years."

But officials of the American Diabetes Assn. cautioned diabetics not to get high hopes about the procedure. "It's nice and it's exciting, but that doesn't mean it is going to work," said physiologist Richard Kahn, the group's chief scientific and medical officer. "Come back in six months. If the patient still [does not need insulin injections] . . . then we have something."

Insulin-dependent or Type 1 diabetes occurs when the body's immune system destroys islet cells in the pancreas. Insulin is normally released by the pancreas when the level of sugars in the bloodstream rises after eating. The insulin enables body cells to use the sugars for energy.

If the body does not receive insulin, it must use stored carbohydrates for energy. The buildup of toxic byproducts from that process eventually leads to coma and death.

Diabetes is treated with insulin obtained from cows or pigs or with human insulin produced by the biotechnology industry. But because insulin is injected periodically, the levels of blood sugar go through wide variations. Many researchers believe that these concentration swings cause the long-term complications of diabetes, including kidney malfunction, nerve damage in the limbs and blindness.

Pancreas transplants have been relatively successful in treating diabetes, and transplants of isolated islets have shown recent promise. But there are not sufficient donors to treat even a small fraction of diabetics, and recipients have to receive immunosuppressive drugs for the rest of their lives to prevent rejection of the grafts.

Researchers have speculated for at least 25 years that such immune attacks could be foiled by enclosing the islets in a porous membrane that would let in nutrients that nourish the cells and permit insulin to be released into the body. At the same time, the membrane would shield the implanted islet cells from attacks by the immune system. Such an approach would permit the use of islets from unrelated donors—or from animals—without the need for immunosuppression.

But the idea, conceptually simple, has proved immensely difficult in practice. Plastic implants in dogs and other large animals have quickly become overgrown with the recipient's cells, cutting off the supply of nutrients and killing the implanted cells within two to four weeks.

The procedure has been attempted in humans at least three times—twice in Italy and once in France. None of the three patients were freed from their insulin dependence, said Dr. David Sharp of Washington University in St. Louis, and the implanted cells died when the capsules became clogged.

Soon-Shiong developed a membrane material based on alginic acid, a polymer isolated from seaweed that is used as a thickener in ice cream. A similar membrane was used in the Italian experiments, but Soon-Shiong said that he discovered an impurity in those preparations that caused the membrane to be clogged.

Membranes prepared without the impurity cured diabetes in dogs and survived for at least two years without becoming clogged, he said. A report of those results will appear next month in the Proceedings of the National Academy of Sciences.

For his first patient, Soon-Shiong chose Craig, a former mechanic and sheriff's aide in Riverside County and Costa Mesa who developed diabetes at age 8. Craig's kidneys failed in 1988 and one was replaced by a donated organ from his brother eight months later.

Craig has been unemployed for seven years because of nerve damage in his legs and failing eyesight. Doctors do not know if the procedure will alleviate any of those symptoms.

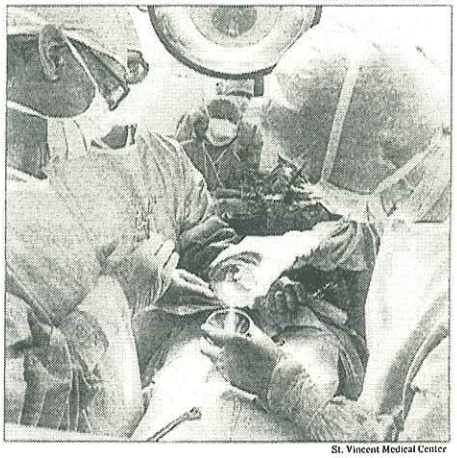
In the 30-minute transplant, performed May 6, Soon-Shiong and his colleagues cut a small slit in Craig's abdomen and poured in eight ounces of encapsulated islets—about 680,000—that had been isolated from cadavers. The capsules become attached to a flap of tissue, called the omentum, just below the skin.

Two days later, Craig ate his first breakfast in 30 years without an accompanying insulin injection. "The experience was terrific," he said at a news conference.

Although the implanted cells are producing insulin, Craig's physicians are still giving him small quantities of insulin, about 20% of his requirement before the surgery, so that the cells are not overly stressed. Soon-Shiong said he hopes to wean Craig from insulin over the next three weeks.

Soon-Shiong has permission from the U.S. Food and Drug Administration to perform 19 more implants. He hopes to do the next one in July, and about one per month thereafter.

All recipients will be St. Vincent diabetic patients who have had a kidney transplant and are receiving immunosuppressive drugs—assuring in the first phase of the trial that the capsules will not be rejected. If the first phase is successful, he said, he will try the procedure in patients who are not receiving immunosuppressive drugs.



St. Vincent Medical Center

Landmark Operation

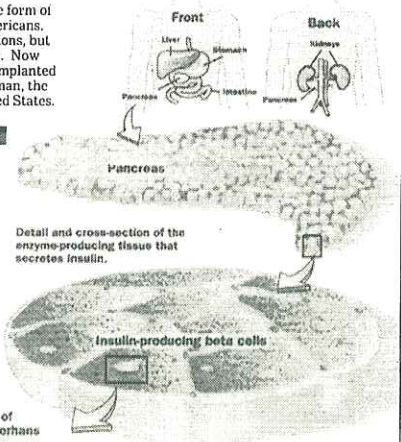
Physicians at St. Vincent Medical Center have begun the first human trials in the United States of an artificial pancreas to treat insulin-dependent diabetics. The artificial pancreas was implanted last week in the abdomen of 38-year-old Steven Craig of Lake Isabella, who has been diabetic for more than 30 years. **The operation,** left, **was the first of 20 such implants the hospital is planning** over the next two years.

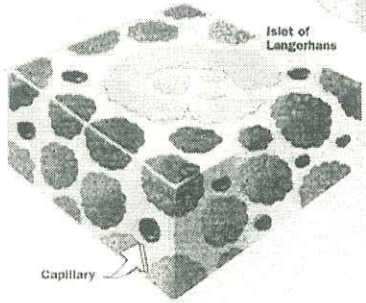
New Procedure to Fight Diabetes

Type 1, or juvenile, diabetes is the most severe form of the disease, affecting more than a million Americans. Those diabetics are treated with insulin injections, but there are side effects, and effectiveness varies. Now surgeons at St. Vincent Medical Center have implanted encapsulated human islets in a Lake Isabella man, the first human trials of this approach in the United States.

HOW A NORMAL PANCREAS FUNCTIONS

- Tiny cell clusters called islets of Langerhans secrete insulin, which enables the body to use and store sugars in the blood. The body typically has about 1 million islets, making up only 2% of the mass of the pancreas. The other 98% secretes digestive enzymes.
- Islets comprise four types of cells. The most common type, beta cells, secrete insulin. The others secrete hormones that regulate insulin use.
- Diabetes results when the body attacks and destroys beta cells. Without insulin, the body can no longer properly use and store sugars from food.





HOW THE NEW GRAFT WORKS

- Islets are separated from cadaver pancreases and encapsulated in a porous membrane that allows nutrients in and insulin and wastes out, while shielding the cells from attack by the immune system.
- About 680,000 encapsulated islets—about eight ounces worth, the equivalent of half a pancreas—are infused into the abdominal cavity through a small slit. The procedure takes about 30 minutes. Physicians hope the islets will survive indefinitely.
- Because the islets are encapsulated, the patient should not require immunosuppressive drugs.

ROB HERNANDEZ / Los Angeles Times

Reprinted from THE LANCET, *April 16 1994, pp. 950–951*

Short reports

Insulin independence in a type 1 diabetic patient after encapsulated islet transplantation

Patrick Soon-Shiong, Roswitha E Heintz, Noma Merideth, Qiang X Yao, Zhiwen Yao, Tianli Zheng, Michael Murphy, Molly K Moloney, Marcia Schmehl, Michael Harris, Robert Mendez, Raphael Mendez, Paul A Sandford

Identification of a biocompatible immunoprotective membrane to prevent graft rejection remained elusive until the development of microcapsules formulated in alginate high in guluronic acid. We report insulin independence in a type 1 diabetic patient after encapsulated islet transplantation. Encapsulated human islets were injected intraperitoneally in a diabetic patient with a functioning kidney graft. Insulin independence with tight glycaemic control was demonstrated 9 months after the procedure. These results warrant a trial of a high dose of encapsulated islets in early-onset diabetic patients.

Lancet 1994; **343:** 950–51

Islet transplantation for type 1 diabetes is disappointing,[1] despite use of multiple immunosuppressive regimes. An alternative to overcome rejection is immunoprotection of the insulin-secreting islets in a semi-permeable alginate-polylysine membrane.[2] The technology has failed to advance into large animal models[2–4] because mechanically unstable membranes, formulated from alginate rich in mannuronic acid, stimulated fibrosis of the capsule via cytokine release.[5,6] We formulated microcapsules with purified alginate with a high guluronic acid content that had improved biocompatibility,[6] mechanical stability, and adequate porosity, which allowed appropriate insulin release from intraperitoneally transplanted human and rat islets in response to systemic glycaemic challenges.[7,8] We could reverse diabetes by intraperitoneally transplanted encapsulated islets in the large animal model[9] with long-term (up to 2 years) islet function after transplantation in spontaneous diabetic dogs even after cessation of all immunosuppression.[10] The safety and efficacy of multiple retransplantation in these diabetic dogs, with no chronic toxicity, was established. We obtained regulatory and institutional approvals for the first human trial.

The patient is a 38-year-old man who has had insulin-dependent diabetes for 30 years, requiring a mean of 0·7 (SE 0·01) U insulin per kg per day (45–50 U daily). The patient had severe complications, including lower extremity peripheral neuropathy (daily, sharp shooting pains of the left lower foot with progressive sensory loss), foot ulcers, retinopathy, and end-stage renal failure resulting in a living-related kidney transplantation. His renal function was stable (serum creatinine 8·8 μmol/L) on low-dose maintenance immunosuppression of cyclosporin and azathiopine 50 mg daily. Our patient did not receive the induction immunotherapy routinely prescribed in trials of unencapsulated islets, and his low-dose maintenance cyclosporin was unchanged during follow-up. Thus, while further trials on non-immunosuppressed patients are needed to demonstrate the immunoprotectivity of the capsules without immunosuppression, as has been shown in the large animal studies,[10] we have demonstrated immunoprotectivity of the capsule under these low-dose conditions.

Human islets were isolated from eight cadaveric donor pancreases by standard collagenase digestion and purified by gradient separation. An islet purity of 85% was obtained with a yield of 1166 999 (actual count) or 960 331 (150 μm equivalent count). After a mean culture period of 22 (SE 16) days, 678 000 encapsulated islet equivalents with a mean insulin stimulation index of 30 (11) were pooled for transplantation. Via a 2 cm midline abdominal incision, the encapsulated islets at 9957/kg were transplanted into the peritoneal space. On the basis of our pre-clinical data, we estimate that a full therapeutic dose of encapsulated islets would be 20 000 per kg. 6 months after the initial dose of about 10 000 islets per kg, the patient received a supplemental dose of 5000 islets per kg as part of a dose-escalation study.

To date, the patient has had no adverse effects. Despite significant reduction in insulin requirements, bodyweight has remained unchanged (69·5 kg). Since the procedure, he has not reported any episode of symptomatic hypoglycaemia. Out of 1560 glucose measurements over the 9 month post-transplant period, only 2 were under 50 mg/dL (table).

Insulin secretion from the transplanted cells was noted within 24 h of transplantation. Despite the sub-clinical dose of encapsulated islets, the patient maintained a stable daily mean blood glucose (table), with less lability relative to pretransplant levels while on a much reduced insulin dose (0·2 U/kg per day). Basal C-peptide secretion increased with the drop in insulin requirements, from under 0·1 ng/mL pretransplant to 0·6 ng/mL post-transplant, which confirms sustained insulin secretion from the encapsulated islets. After the supplemental dose of islets, insulin requirements were reduced further to 1–2 U per day, with an elevation of basal C-peptide to 1·0 ng/mL. In the ninth month, exogenous insulin could be discontinued and his 24 hour mean blood glucose remained stable. Pro-insulin levels during this period of insulin independence were high (1·24 ng/mL), suggesting that this dose of 15 000 islets per

	Pretransplant	Post-transplant (months)				
		2	4	6	8	9
Blood glucose						
No of observations	60	182	114	117	120	114
Daily mean (SE) (mg/dL)	146 (7·1)	153 (4·94)	150 (4·95)	129 (2·61)	144 (4·51)	135 (3·86)
< 50 mg/dL episodes (%)	0	0	0	0	0·83	0
> 200 mg/dL episodes (%)	11·7	16·48	15·79	1·71	10·00	6·14
M-value*	4·35	4·83	3·60	0·20	3·04	1·16
Mean (SE) daily insulin requirement (U/kg)	0·69 (0·01)	0·21 (0·01)	0·27 (0·00)	0·25 (0·01)	0·07 (0·01)	0
Metabolic indices						
Fasting pro-insulin (ng/mL)	<0·04	..	0·36	0·28	0·59	1·24
Fasting C-peptide (ng/mL)	0·1	0·4	0·6	0·6	1·0	..
Haemoglobin A_{1c} (%)†	9·3	8·2	7·6	7·8	7·8	7·9
Glycosylated albumin (%)†	10·6	4·4	4·3	5·1	5·1	5·3

*Normal = 120 mg/dL. †% of total haemoglobin or albumin, respectively.

Table: **Islet function and glycaemic control after encapsulated islet transplantation**

kg was still sub-critical, and that the islets were being stressed to maintain insulin independence.

For the first 3 months, serum glucose was monitored seven times a day. Without regular insulin pre-prandially, blood glucose rose from a pre-prandial 82 (2·7) mg/dL to 149 (10·0) mg/dL 2½ hours post-prandially (n = 19), which again confirms the production of endogenous insulin from the encapsulated islets. When the patient was given a minimum dose of only 0·5 U insulin pre-prandially, pre-prandial (138 [4] mg/dL) and post-prandial (142 [5] mg/dL) serum glucose were similar (58 observations).

The M-value provides an index of glycaemic control and is a measure of how far a given glucose level deviates from a given standard. With a standard blood glucose of 120 mg/dL, the patient had more than 100 fold improvement in M-value at 6 months (0·20) compared with the pretransplant value of 4·35, indicating significantly less glycaemic lability over 24 hour periods since the transplantation. These improvements were corroborated by improvements in glycosylated serum albumin and glycosylated haemoglobin concentrations. Glycosylated serum albumin decreased from 10·6% pretransplant to 5·1% at 6 months and to 5·3% at 9 months, while glycosylated haemoglobin fell from 9·3 to 7·8% (table).

The sharp shooting pains in his left lower foot, which occurred constantly pretransplant, abated in the post-transplant period. Electromyography studies confirmed improvement in axonal nerve function (continued bilateral increases of amplitude of peroneal motor latencies 6 months post-translant: from 45 to 187 mV on the left and from 200 to 425 mV on the right). The left foot ulcer, which had required about 3 months to heal pretransplant, recurred on week 10 post-transplant. This ulcer healed within 7 days.

Throughout the 9 month follow-up renal function has remained stable (serum creatinine 62–115 μmol/L).

A quality of life questionnaire was completed by the patient pretransplant, and at 3 and 6 months post-transplant. He reported improvement in various aspects, including increased energy, ability to walk further, and general feeling of improved health. For the first time in a decade he is now in full-time employment.

Our studies in diabetic dogs[9,10] demonstrated that 20 000 encapsulated islets per kg were needed to achieve insulin independence. The optimum human intraperitoneal dose is obviously unknown, and further studies are needed to establish this value. These results warrant a trial of a high dose of encapsulated islets in early-onset diabetic patients.

We thank Ms Frederique Strohm, Dr Neil Desai, Mr Andrew Sojomihardjo, Dr Edward Feldman, Dr Richard Nelson, Dr Gudmund Skjak-Braek, Dr Olav Smidsrod, and Dr Terje Espevik for their input, and the Foundation for Transplant Research and St Vincent Medical Centre for supporting this study.

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